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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/506,414	HUNG ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *22-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☒ Claim(s) *1, 9-10, 12 and 14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Amendments

In the reply filed December 12, 2006, Applicant has withdrawn Claims 22-27 and amended Claims 1, 9 and 12-15. Claims 1-21 are under consideration.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements January 26, 2007 that has been considered. The signed and initialed PTO Form 1449 is mailed with this action.

Claim Objections

1. **Claims 1, 9-10, 12 and 14 are newly objected to because of the following informalities:**

With respect to Claims 1, 9 and 12, the claims have been amended to identify NF2 as a gene that is mutated in the claimed invention. However, the claims do not first identify the gene by its complete name prior to using its acronym. The abbreviation should be spelled out in the first appearance of the claims and should be followed by the abbreviation in parentheses, e.g. Epidermal Growth Factor (EGF). Furthermore, the phrase 'mutant NF2 gene' should be amended to include the article "a", as in 'a mutant NF2 gene'.

With respect to Claim 10, it appears that a typographical error has occurred. The term "adenovirus EA" is incorrect. The art recognizes the adenoviral immortalizing gene to be denoted as "E1A" (Katakura et al, 1998, *of record). In the interest of compact prosecution, the Examiner interprets the term "EA" to be "E1A".

The noun 'gene' in Claims 12 and 14 do not agree in number with the respective pronouns 'E6 and E7'. See for example, Claim 3.

Appropriate correction is required.

Specification

2. **The prior objection to the disclosure is withdrawn** because Applicant has amended the specification to correct the literature citation.

3. **The disclosure is newly objected to because of the following informalities:** it appears that a typographical error has occurred (pg 8, line 10). The term "adenovirus EA" is incorrect. The art recognizes the adenoviral immortalizing gene to be denoted as "E1A" (Katakura et al, 1998, *of record). In the interest of compact prosecution, the Examiner interprets the term "EA" to be "E1A".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. **The prior rejection of Claims 1-21 under 35 U.S.C. 112, first paragraph is withdrawn** because Applicant has i) amended the claims to remove the 'non-tumorigenic' limitation of the claimed immortalized cells, and ii) amended the specification to address the availability of the #PTA-4544 cells.

5. **Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph**, while being enabling for:

A) A method for producing an immortalized human Schwann or Schwannoma cell line comprising the steps of:

a) providing a primary cell culture of human Schwann or Schwannoma cells, and

b) introducing a polynucleotide comprising an exogenous immortalizing gene into said cells, and

c) selecting for immortalized cells that express the exogenous immortalizing gene and retain phenotypic properties of Schwann or Schwannoma cells, said phenotypic properties comprising rapid growth and antigen-positive for S100,

B) An isolated, immortalized human Schwannoma cell line which expresses an exogenous immortalizing gene and retains the phenotypic properties comprising rapid growth, antigen-positive for S100 and a mutant NF2 gene,

C) An isolated, immortalized human Schwannoma cell line actively expressing the E6 and E7 genes of human papilloma virus 16, wherein the immortalized cell line has the phenotypic characteristics comprising rapid growth, antigen-positive for S100 and a mutant NF2 gene,

D) An isolated HEI-193 human Schwannoma cell line actively expressing the E6 and E7 genes of human papilloma virus 16, deposited as ATCC Accession #PTA-4544, and

E) A method for determining the effect of a pharmacological agent on an isolated, immortalized human Schwannoma cell line which expresses an exogenous immortalizing gene and retains the phenotypic properties comprising rapid growth, antigen-positive for S100 and a mutant NF2 gene, said method comprising the steps of:

a) contacting said cell line with said pharmacological agent, and

b) determining the effect of said pharmacological agent on said cell line,

does not reasonably provide enablement for:

i) isolated immortalized human Schwann cell lines comprising a mutant NF2 gene, and

ii) method steps for selecting immortalized cells that retain phenotypic property of Schwann or Schwannoma cells, said phenotypic property being a mutant NF2 gene.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to an immortalized human Schwann or Schwannoma cell line that comprises a mutation in the neurofibromatosis 2 (NF2) gene. At issue for the instant rejection is the requirement for the existence of an NF2 mutation in the immortalized Schwann and Schwannoma cells, absent an artisan-required step of introducing the mutation into those cells that did not have pre-existing NF2 mutations.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The breadth of the claim is exceptionally large for encompassing an enormous genus of non-mutant Schwann cells and Schwannoma cells comprising at least one genetic alteration obtained from any member of the human population, from which the artisan may then immortalize the isolated cells. The use of the suffix "-oma" as commonly used in the art denotes a tumorous cell (www.medterms.com, last visited April 20, 2007) which has distinctly different genetic and phenotypic properties than normal, non-transformed, non-tumorous cell.

The inventive concept in the instant application is the isolation of a human Schwannoma cell line from patients suffering neurofibromatosis, wherein the tumorigenic Schwannoma cells comprise a pre-existing mutation in the endogenous NF2 gene.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The art teaches that normal, non-mutant Schwann cells may be isolated from mammalian tissues and immortalized *in vitro* (Peden et al, Annual N.Y. Acad. Sci 605: 286-293, 1990) by

introducing an exogenous immortalizing gene into the non-mutant Schwann cell. For example, Katakura et al (*of record) reviewed the knowledge in the art, wherein the art has long used nucleic acid vectors encoding SV40 large T antigen, HPV E6 and E7 proteins and adenovirus E1A proteins to immortalize mammalian cells. The art does not teach that the process of immortalization *a priori* yields mutations in the NF2 gene.

The art is silent with respect to using a mutated NF2 gene to immortalize human Schwann cells. Rather, Rosenbaum et al (Neurobiology of Disease 5: 55-64, 1998) teach that "[A]lthough NF2 Schwann cells [primary cultures obtained from NF2 patients] still proliferate at higher passages, cell numbers could not be expanded infinitely. During long-term incubation it seems that NF2 Schwann cells change in morphology, grow extremely large, flatten, and contain multiple nuclei." (pg 59, col.2) Thus, one of ordinary skill in the art would reasonably conclude that NF2 mutations are insufficient to immortalize primary, non-mutant human Schwann cells.

The level of skill for the ordinary artisan in the field of cellular immortalization is considered high, as this technique has been practiced on a multitude of cell types obtained from a broad genus of vertebrate organisms. Furthermore, the art recognizes that human Schwannoma cells do not necessarily comprise NF2 mutations, but may comprise mutations in other genes, such as NF1 (Zwarthoff, Pathol. Res. Pract. 192(7):647-57, 1996; Abstract only). Thus, the art recognizes considerable uncertainty in the step of cellular immortalization to necessarily yield a mutation in the NF2 gene. Rather, to fulfill the instant limitation, the artisan must either introduce the NF2 mutation directly, or acquire cells that have pre-existing NF2 mutations.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The specification discloses the immortalization of human Schwannoma cells from a patient suffering from mutation in the NF2 gene.

The specification is silent regarding the type and structure of nucleic acid required to comprise an NF2 mutation for the immortalization process of non-mutant human Schwann cells. Similarly, the specification is silent regarding the frequency of occurrence of NF2 mutations in an immortalized Schwann or Schwannoma cell line that had no pre-existing NF2 mutation.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that the enormous genus of human Schwann or Schwannoma cells that do not comprise a pre-existing NF2 mutation will, in fact, give rise to an NF2 mutation in the absence of an artisan-required method step to specifically introduce the NF2 mutation.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to:

A) A method for producing an immortalized human Schwann or Schwannoma cell line comprising the steps of:

a) providing a primary cell culture of human Schwann or Schwannoma cells, and

b) introducing a polynucleotide comprising an exogenous immortalizing gene into said cells, and

c) selecting for immortalized cells that express the exogenous immortalizing gene and retain phenotypic properties of Schwann or Schwannoma cells, said phenotypic properties comprising rapid growth and antigen-positive for S100,

B) An isolated, immortalized human Schwannoma cell line which expresses an exogenous immortalizing gene and retains the phenotypic properties comprising rapid growth, antigen-positive for S100 and a mutant NF2 gene,

C) An isolated, immortalized human Schwannoma cell line actively expressing the E6 and E7 genes of human papilloma virus 16, wherein the immortalized cell line has the phenotypic characteristics comprising rapid growth, antigen-positive for S100 and a mutant NF2 gene,

D) An isolated HEI-193 human Schwannoma cell line actively expressing the E6 and E7 genes of human papilloma virus 16, deposited as ATCC Accession #PTA-4544, and

E) A method for determining the effect of a pharmacological agent on an isolated, immortalized human Schwannoma cell line which expresses an exogenous immortalizing gene

and retains the phenotypic properties comprising rapid growth, antigen-positive for S100 and a mutant NF2 gene, said method comprising the steps of:

a) contacting said cell line with said pharmacological agent, and

b) determining the effect of said pharmacological agent on said cell line,

is proper.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention..

6. **The prior rejection of Claims 1, 12-14 and 17 under 35 U.S.C. 112, second paragraph, is withdrawn** because Applicant has amended the claims to address the issues regarding the phrases "phenotypic properties" and "phenotypic characteristics".

7. **The prior rejection of Claim 14 under 35 U.S.C. 112, second paragraph, is withdrawn** because Applicant has amended the claim to address the issues regarding the limitation of a cell line having "the identifying characteristics" of ATCC #PTA-4544.

8. **Claim 14 is newly rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites the phrase "substantially pure". The obvious question becomes: pure from what? Neither the claims nor the specification define the metes and bounds of the recited purity. Furthermore, the use of the alternative term "or" introduces ambiguity into the identity of the cell line. One of ordinary skill in the art would reasonably conclude that a cell is either a Schwann cell or a Schwannoma cell, but not both. The use of the suffix "-oma" as commonly used in the art denotes a tumorous cell (www.medterms.com, last visited April 20, 2007) which has distinctly different genetic and phenotypic properties than normal, non-transformed, non-

tumorous cell. The specification discloses that the HEI-193 cells, deposited as ATCC Accession #PTA-4544, are derived from human Schwannoma cells (pg 13, Examples; pg 3, lines 9-10).

The Examiner suggests the claim be amended to read, "An isolated HEI-193 human Schwannoma cell line actively expressing the E6 and E7 genes of human papilloma virus 16, deposited as ATCC Accession #PTA-4544."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. **Claims 1-2 and 6 are newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Peden et al (Annual N.Y. Acad. Sci 605: 286-293, 1990)

Peden et al teach a method to immortalize primary rat Schwann cells with a plasmid encoding an exogenous SV40 T antigen oncogene, wherein the immortalized Schwann cells have retained the phenotypic properties comprising rapid growth (pg 291, Table 1) and antigen-positive for S100 (pg 290, line 4). Peden et al do not teach a method of immortalizing human Schwann cells.

It would have been obvious to substitute the rat Schwann cells immortalized by the method taught by Peden et al with the human Schwannoma cells with a reasonable chance of success because both cells types are mammalian Schwann cells. Absent evidence to the contrary, there is nothing non-obvious for substituting Schwann cells from a rodent with Schwann cells from a human.

An artisan would be motivated to substitute the rat Schwann cells for human Schwann cells because Peden et al suggest that "[W]e are applying this approach to generate analogous

cell lines from the peripheral nerves of other species such as mouse and human." "The ability to produce large numbers of human Schwann cells from nerve biopsy and to analyze their biochemical properties would be of enormous value in identifying the cellular abnormalities that result in demyelinating disease. (pg 293, ¶2).

Thus, the invention as a whole is *prima facie* obvious.

10. **Claims 3-5 and 7-8 are newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Peden et al (Annual N.Y. Acad. Sci 605: 286-293, 1990) as applied to Claim 1 above, and in further view of Roque et al (Exp. Eye Res. 64: 519-527, 1997), Schlegal (U.S. Patent No. 5,376,542) and Katakura et al (1998, *of record).

The prior cited art does not teach the immortalizing polynucleotide to be from adenovirus or human papilloma virus. However, at the time of the invention, Roque et al summarized the general knowledge in the art that recombinant HPV type 16 viruses encoding the E6 and E7 proteins have long been used in the art to immortalize mammalian cell types, including human keratinocytes, fibroblasts and mammary epithelial cells (pg 526, col. 1, ¶2). Roque et al teach the use of recombinant, replication defective retroviral vector encoding the HPV-16 E6 and E7 proteins to immortalize rat Muller cells, a type of neural glial cell, from a mixed retinal cell culture (pg 520). Similarly, Schlegal disclosed that [retroviral] vectors containing HPV-16, 18, 31, 33 or 35 E6 and E7 genes may be used to immortalize cells (col. 5, lines 63-64; col. 6, lines 38-39). Furthermore, Katakura et al reviewed the knowledge in the art, wherein the art has long used recombinant viral vectors encoding SV40 large T antigen, HPV E6 and E7 proteins and adenovirus E1A proteins to immortalize mammalian cells.

It would have been obvious to substitute the immortalizing gene of Peden et al to be either the HPV-16 E6 and E7 proteins or adenovirus E1A protein as taught by Rogue et al, Schlegal et al and Katakura et al with a reasonable expectation of success because the art has long recognized these proteins having immortalizing properties "to generate cell lines from cell types that are not abundant or are difficult to obtain in pure form in primary culture, are in short supply as human cells, and/or have brief lifetimes in culture." (Katakura, pg 70) Absent evidence to the contrary, nothing non-obvious is seen with replacing one immortalizing gene with another immortalizing gene. An artisan would be motivated to substitute one immortalizing gene for

another as part of normal experimental optimization of conditions, e.g. so as to fulfill the size constraint needs of the immortalizing vector.

Thus, the invention as a whole is *prima facie* obvious.

11. **Claim 9 is newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Peden et al (Annual N.Y. Acad. Sci 605: 286-293, 1990) and Rosenbaum et al (Neurobiology of Disease 5: 55-64, 1998).

Peden et al teach primary rat Schwann cells immortalized with a plasmid encoding an exogenous SV40 T antigen oncogene, wherein the immortalized Schwann cells have retained the phenotypic properties comprising rapid growth (pg 291, Table 1) and antigen-positive for S100 (pg 290, line 4).

Peden et al do not teach immortalized human Schwannoma cells comprising NF2 mutations; however, at the time of the invention, Rosenbaum et al taught the isolation of NF2 Schwannoma cells from human patients, wherein said cells comprise the phenotypic characteristics of mutations in the NF2 gene (pg 58, Table 1), expressing the S100 marker (pg 59, Table 2) and increased growth rates (pg 59, col. 1). Rosenbaum et al taught a method of screening Schwannoma cell lines for NF2 mutations (pg 58, col. 1, Mutation and LOH Analysis). Rosenbaum et al taught that as the NF2 Schwannoma cells were passaged in culture, their relative purification from contaminating fibroblasts increased (pg 57, col. 2; pg 59, Table 2).

It would have been obvious to substitute the rat Schwann cells immortalized by the method taught by Peden et al with the human Schwannoma cells taught by Rosenbaum et al with a reasonable chance of success because both cells types are mammalian Schwann cells. Absent evidence to the contrary, there is nothing non-obvious for substituting Schwann cells from a rodent with Schwann cells from a human.

An artisan would be motivated to substitute the rat Schwann cells for human Schwann cells because Peden et al suggest that "[W]e are applying this approach to generate analogous cell lines from the peripheral nerves of other species such as mouse and human." "The ability to produce large numbers of human Schwann cells from nerve biopsy and to analyze their biochemical properties would be of enormous value in identifying the cellular abnormalities that result in demyelinating disease. (pg 293, ¶2). An artisan would be further motivated to

immortalize human NF2 schwannoma cells because Rosenbaum et al teach that "[A]lthough [primary cultures] NF2 Schwann cells still proliferate at higher passages, cell numbers could not be expanded infinitely. During long-term incubation it seems that NF2 Schwann cells change in morphology, grow extremely large, flatten, and contain multiple nuclei." (pg 59, col.2) The art recognizes the lack of an appropriate methodology to reliably examine the function of NF2 in the cells that manifest disease, namely Schwann cells. Furthermore, Rosenbaum et al suggest that the *in vitro* characterization of Schwannoma cells with disease-relevant genetic alterations may shed light directly on effects of these alterations and thus possibly provide crucial clues for understanding genotype–phenotype correlations in NF2. The ability to expand and compare NF2 and control Schwann cells *in vitro* can provide a model with the authentic cell type and genotype for investigation of the pathogenesis of NF2.

12. **Claim 10 is newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Peden et al (Annual N.Y. Acad. Sci 605: 286-293, 1990) and Rosenbaum et al (Neurobiology of Disease 5: 55-64, 1998), as applied to Claim 9 above, and in further view of Katakura et al (1998, *of record).

The prior cited art does not teach the use of an immortalizing polynucleotide from adenovirus or human papilloma virus. However, at the time of the invention, Katakura et al reviewed the knowledge in the art, wherein the art has long used recombinant viral vectors encoding SV40 large T antigen, HPV E6 and E7 proteins and adenovirus E1A proteins to immortalize mammalian cells.

It would have been obvious to substitute the immortalizing gene of Peden et al to be either the HPV-16 E6 and E7 proteins or adenovirus E1A protein as taught by Katakura et al with a reasonable expectation of success because the art has long recognized these proteins having immortalizing properties "to generate cell lines from cell types that are not abundant or are difficult to obtain in pure form in primary culture, are in short supply as human cells, and/or have brief lifetimes in culture." (Katakura, pg 70) Absent evidence to the contrary, nothing non-obvious is seen with replacing one immortalizing gene with another immortalizing gene.

An artisan would be motivated to substitute one immortalizing gene for another as part of normal experimental optimization of conditions, e.g. so as to fulfill the size constraints of the nucleic acid vector.

Thus, the invention as a whole is *prima facie* obvious.

13. **Claim 11 is newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Peden et al (Annual N.Y. Acad. Sci 605: 286-293, 1990) Rosenbaum et al (Neurobiology of Disease 5: 55-64, 1998) and Katakura et al (1998, *of record), as applied to Claims 9-10 above, and in further view of Schlegal (U.S. Patent No. 5,376,542).

The prior cited art does not teach the use of HPV types –31, 33 and 35. However, at the time of the invention, Schlegal disclosed that [retroviral] vectors containing HPV-16, 18, 31, 33 or 35 E6 and E7 genes may be used to immortalize cells (col. 5, lines 63-64; col. 6, lines 38-39).

It would have been obvious to substitute the immortalizing gene of Peden et al or Katakura et al to be either the HPV-31, 33 or 35 E6 and E7 proteins as taught by Schlegal et al with a reasonable expectation of success because the art has long recognized these proteins having immortalizing properties. Absent evidence to the contrary, nothing non-obvious is seen with replacing the E6 and E7 immortalizing genes from any of the recited HPV types because the art recognizes that the E6/E7 genes from each of the viral subtypes has immortalizing properties.

An artisan would be motivated to substitute one immortalizing gene for another as part of normal experimental optimization of conditions, e.g. so as to fulfill the size constraints of the nucleic acid vector.

Thus, the invention as a whole is *prima facie* obvious.

14. **Claims 12-13 are newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Peden et al (Annual N.Y. Acad. Sci 605: 286-293, 1990), Rosenbaum et al (Neurobiology of Disease 5: 55-64, 1998), Roque et al (Exp. Eye Res. 64: 519-527, 1997), Schlegal (U.S. Patent No. 5,376,542) and Katakura et al (1998, *of record), as evidenced by Li et al (Cancer Biotherapy & Radiopharm. 18(5): 829-840, 2003).

Peden et al teach primary rat Schwann cells immortalized with a plasmid encoding an exogenous SV40 T antigen oncogene, wherein the immortalized Schwann cells have retained the

phenotypic properties comprising rapid growth (pg 291, Table 1) and antigen-positive for S100 (pg 290, line 4).

Peden et al do not teach immortalized human Schwannoma cells comprising NF2 mutations; however, at the time of the invention, Rosenbaum et al taught the isolation of NF2 Schwannoma cells from human patients, wherein said cells comprise the phenotypic characteristics of mutations in the NF2 gene (pg 58, Table 1), expressing the S100 marker (pg 59, Table 2) and increased growth rates (pg 59, col. 1). Rosenbaum et al taught a method of screening Schwannoma cell lines for NF2 mutations (pg 58, col. 1, Mutation and LOH Analysis). Rosenbaum et al taught that as the NF2 Schwannoma cells were passaged in culture, their relative purification from contaminating fibroblasts increased (pg 57, col. 2; pg 59, Table 2).

Neither Peden et al nor Rosenbaum et al teach the use of an immortalizing polynucleotide from adenovirus or human papilloma virus. However, at the time of the invention, Roque et al summarized the general knowledge in the art that recombinant HPV type 16 viruses encoding the E6 and E7 proteins have long been used in the art to immortalize mammalian cell types, including human keratinocytes, fibroblasts and mammary epithelial cells (pg 526, col. 1, ¶2). Roque et al teach the use of recombinant, replication defective retroviral vector encoding the HPV-16 E6 and E7 proteins to immortalize rat Muller cells from a mixed retinal cell culture (pg 520), wherein the art recognizes retroviral vectors integrate into the host nuclear genome (see, for example, Li et al, pg 831, col. 2, Infection Efficiency and Integration, and Figure 1, as it relates to the pLXSN recombinant retroviral vector). Similarly, Schlegal disclosed that [retroviral] vectors containing HPV-16, 18, 31, 33 or 35 E6 and E7 genes may be used to immortalize cells (col. 5, lines 63-64; col. 6, lines 38-39). Furthermore, Katakura et al reviewed the knowledge in the art, wherein the art has long used recombinant viral vectors encoding SV40 large T antigen, HPV E6 and E7 proteins and adenovirus E1A proteins to immortalize mammalian cells.

It would have been obvious to substitute the rat Schwann cells immortalized by the method taught by Peden et al with the human Schwannoma cells taught by Rosenbaum et al with a reasonable chance of success because both cells types are mammalian Schwann cells. Absent evidence to the contrary, there is nothing non-obvious for substituting Schwann cells from a rodent with Schwann cells from a human.

An artisan would be motivated to substitute the rat Schwann cells for human Schwann cells because Peden et al suggest that "[W]e are applying this approach to generate analogous cell lines from the peripheral nerves of other species such as mouse and human." "The ability to produce large numbers of human Schwann cells from nerve biopsy and to analyze their biochemical properties would be of enormous value in identifying the cellular abnormalities that result in demyelinating disease. (pg 293, ¶2). An artisan would be further motivated to immortalize human NF2 schwannoma cells because Rosenbaum et al teach that "[A]lthough [primary cultures] NF2 Schwann cells still proliferate at higher passages, cell numbers could not be expanded infinitely. During long-term incubation it seems that NF2 Schwann cells change in morphology, grow extremely large, flatten, and contain multiple nuclei." (pg 59, col.2) The art recognizes the lack of an appropriate methodology to reliably examine the function of NF2 in the cells that manifest disease, namely Schwann cells. Furthermore, Rosenbaum et al suggest that the *in vitro* characterization of Schwannoma cells with disease-relevant genetic alterations may shed light directly on effects of these alterations and thus possibly provide crucial clues for understanding genotype–phenotype correlations in NF2. The ability to expand and compare NF2 and control Schwann cells *in vitro* can provide a model with the authentic cell type and genotype for investigation of the pathogenesis of NF2.

It also would have been obvious to substitute the immortalizing gene of Peden et al to be either the HPV-16 E6 and E7 proteins or adenovirus E1A protein as taught by Rogue et al, Schlegal et al and Katakura et al with a reasonable expectation of success because the art has long recognized these proteins having immortalizing properties "to generate cell lines from cell types that are not abundant or are difficult to obtain in pure form in primary culture, are in short supply as human cells, and/or have brief lifetimes in culture." (Katakura, pg 70) Absent evidence to the contrary, nothing non-obvious is seen with replacing one immortalizing gene with another immortalizing gene.

An artisan would be motivated to substitute one immortalizing gene for another as part of normal experimental optimization of conditions, e.g. so as to fulfill the size constraints of the nucleic acid vector.

Thus, the invention as a whole is *prima facie* obvious.

15. **Claims 15-21 are newly rejected under 35 U.S.C. 103(a)** as being unpatentable over Peden et al (Annual N.Y. Acad. Sci 605: 286-293, 1990) and Rosenbaum et al (Neurobiology of Disease 5: 55-64, 1998), as applied to Claim 9 above, and in further view of Einheber et al (Journal of Cell Biology 129(2): 443-458, 1995), Bonetti et al (J. Neuropathol. Exp. Neurol. 59(1): 74-84, 2000) and Steele et al (Carcinogenesis 21(1): 63-67, 2000).

The prior cited art does not teach a method using the immortalized cells for determining the effect of a pharmacological agent on human Schwann or Schwannoma cells.

However, at the time of the invention, Einheber et al taught the evaluation of numerous phenotypic characteristics in primary rat Schwann cells in response to the administration of TGFβ-1, alone or in combination, with the chemical drug forskolin, such as expression of Schwann cell markers, myelination of neurons in co-culture, changes in basal lamina formation, proliferation and expression growth factor receptors (see entire document). TGFβ-1 is well known in the art to be a growth factor and to have profound effects on Schwann cell proliferation and differentiation that are context dependent, such as increasing the expression of NCAM cell adhesion molecule and the SCIP transcription factor (page 444, column 2, lines 38-62). Forskolin is known in the art to elevate cyclic AMP levels, and depending on the concentration, may increase Schwann cell proliferation or stimulate Schwann cell differentiation and myelination. Forskolin also induces expression of the SCIP transcription factor, which in turn inhibits expression of the p75 nerve growth factor receptor and the myelin protein P0 (page 444). Similarly, Bonetti et al taught the evaluation of numerous phenotypic effects when treating primary human Schwann and Schwannoma cells with the TNFα cytokine, alone or in combination with, the chemical drug acetylsalicylic acid, such as changes in cellular gene expression such as Schwann cell transcription factors, signaling molecule, growth factor, growth factor receptor, myelination of neurons in co-culture, proliferation, expression of growth factor receptors, and apoptotic events (see entire document). Likewise, Steele et al taught several *in vitro* bioassays, including inhibiting carcinogen binding to DNA, the generation of free radicals, anchorage-independent growth inhibition, focus formation inhibition, mammary organ culture alveolar nodule inhibition and induction of cellular enzymes-an activity that potentially identifies chemopreventative agents to assess possible cancer chemoprotective effects due to exposure of

black and green tea extracts, and the chemicals therein as applied to several human and murine cell types (see entire document).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cell types as taught by Einheber et al, Bonetti et al and Steele et al with the immortalized human Schwann or Schwannoma cells of the prior cited art with a reasonable chance of success because Einheber et al and Bonetti et al demonstrate that Schwann cells may be used *in vitro* to assay diverse phenotypic responses, such as viability, morphology, differentiation, proliferation and gene expression, upon exposure to an exogenous compound. Furthermore, the Applicant's own admission that the numerous assays and techniques to measure genotoxicity, DNA adduct formation, mutagenicity, cell transformation and/or cytotoxicity, cell growth and colony formation are standard techniques well known in the art (page 8, lines 25-29, page 9, lines 9 and 20). An artisan would be motivated to use the immortalized human Schwann or Schwannoma cells of the instant application in diverse pharmacology assays because the invention enables others to perform studies regarding Schwann cell biology and development, such as studying gene-gene interactions, mechanisms of mutagenesis and tumorigenesis of Schwannoma cells, and assess possible therapeutic interventions, such as drugs that reduce the growth rate of the tumors, that would not have been possible using primary, mortal Schwann cell cultures or non-Schwann cell types.

Thus, the invention as a whole is *prima facie* obvious.

Conclusion

16. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kevin K. Hill

Q. JANICE LI, M.D.
PRIMARY EXAMINER